

Intensified Cytotoxic Treatment and Stem Cell Transplantation for Myelodysplasia

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Introduction

The myelodysplastic syndromes (MDS) comprise a rather heterogeneous group of clonal bone marrow failure syndromes, characterized by different levels of uncoupling of proliferative and differentiative responses of hematopoietic stem cells, leading to hypercellular marrows with peripheral cytopenias, qualitative abnormalities in erythroid, granulocytic and megakaryocytic series, and increased transformation into acute leukemia.

The putative rise in overall incidence rates of MDS—possibly related to environmental factors—has been a matter of much debate. The improved understanding of the molecular mechanisms underlying MDS pathophysiology has not only led to increased and earlier detection, but also to considerable bias in epidemiological studies. However, a true, steady increase and possibly a gradual shift towards younger age categories cannot be denied. Hence, an increased demand for improved therapeutic strategies, including intensified cytotoxic treatment with or without stem cell support.

Therapeutic strategies have historically been inspired by either “missionary” approaches, i.e. converting (pre)malignant cells into normal behaviour, or by “crusader” tactics, i.e. destroying non-compliant elements at the expense of innocent bystanders. Transplantation of allogeneic stem cells has thereby proven to be the only truly curative treatment option, but at the expense of considerable transplant related mortality.

The elaboration of risk-adapted treatment algorithms has been much facilitated by the publication of the International Prognostic Scoring System (IPSS), which uses marrow blast percentage, cytogenetic data and number of cytopenias to delineate low, intermediate (1 and 2) and high risk categories.

While not much controversy will exist on the treatment options for the older low risk patient or the younger high risk patient, the IPSS has intensified the discussion around optimal treatment for younger low or intermediate, and older (>50 years old) intermediate and high risk patients.

Intensive cytotoxic treatment.

In the early 1980s the feasibility of AML-type chemotherapy for MDS was demonstrated. Subsequently, several studies showed complete remission rates varying from 15% to 64%. On average CR rates in MDS are lower than those in de novo AML patients, treated with similar or identical, mostly Ara-C containing regimens. Two reasons account for the lower response rates: prolonged cytopenia, leading to higher early death rates, and increased drug resistance, mostly mdr-

P-glycoprotein related.

Factors predictive for reaching CR include younger age, RAEB or RAEB-T versus AML following MDS, primary versus therapy-related MDS, the absence of cytogenetic abnormalities, and the use of newer anthracyclines (e.g. idarubicin), which are less affected by P glycoprotein.

Maintaining remission after CR remains a major problem. The median duration of disease-free survival (DFS) rarely exceeds 12 months. For patients achieving remission, age seems to become less important as a predictor for overall and DFS. This may have much to do with initial performance status. Unfavourable cytogenetics are the major determinant for poor survival after intensive chemotherapy.

In a recent analysis of long-term survival of MDS-patients achieving either CR or PR after intensive chemotherapy, the French group showed a >4 years survival of 14%, half of which are still in CR and probably cured. These long-term survivors were characterized by a significantly higher incidence of RAEB-T at diagnosis and with normal or favourable cytogenetic findings. Earlier treatment in the course of the disease also seemed to confer a better prognosis.

This indicates that at least some patient categories—even some that only achieve PR—may benefit from intensive cytotoxic treatment.

At present it is unclear whether newer therapeutic regimens containing fludarabine or decitabine may give higher CR rates and more prolonged remission duration. Preliminary results of ongoing studies seem to point in that direction.

The use of myeloid growth factors—G-CSF or GM-CSF—may decrease the duration of granulocytopenia, but does not seem to increase survival. The concept of priming, i.e. concomitant use of growth factors with chemotherapy to trigger leukemic cells into cycle making them more vulnerable to chemotherapy, has proved to be disappointing.

It remains to be proven if the advent of newer cytokines, e.g. SCF or thrombopoietin, can alleviate treatment related toxicity and diminish early death rates.

The small percentage of long-term survivors after intensive therapy obviates the need for innovative consolidation approaches.

Allogeneic stem cell transplantation

Several reports have indicated that allogeneic stem cell transplantation can lead to prolonged long-term DFS and cure in a selected group of MDS patients.

The results of allo transplant are best in younger patients with untreated or minimally treated RA, as well as stable RAEB. Results of registry analyses have underscored that the status of the underlying disease at transplant has a

major influence on survival. EBMT data disclosed DFS rates of 46%, 35%, 27% and 0% at 5 years for, respectively, RA/RARS, RAEB, RAEB-T and sAML. A multivariate analysis showed that the presence of bone marrow blasts > 30% negatively correlated with overall survival. Patients achieving CR seem to do much better than patients refractory to aggressive chemotherapy, with very few of the latter surviving after BMT. Patients with MDS or AML, related to previous chemo-radiotherapy, fare generally worse, especially if no CR can be obtained with induction chemotherapy.

A recent overview of the Seattle experience in 251 patients with a median follow-up of 3.7 years, showed an actuarial DFS rate of 41%, with a cumulative relapse rate of 17%. The 3-year cumulative incidence of nonrelapse mortality was 42%. A multivariable analysis again pointed towards increased age, advanced disease status, poor cytogenetics, and therapy related disease as negative risk factors for both early death and relapse.

Many other groups also have been disappointed by the high to very high non relapse mortality in their patients.

Unfortunately many MDS-patients lack a suitable HLA-identical sibling donor. The results of transplants using alternative, partially matched family donors and phenotypically matched unrelated donors, are unsatisfactory and display a staggering transplant mortality of about 50%. The probability of DFS is only 18 to 30%, depending largely on age and interval between diagnosis and transplant.

Controversies in allogeneic transplantation for MDS

Many investigators will regard the high to very high allo-transplant related mortality rates as unacceptable.

Best results with allo transplant are obtained in younger patients early in the course of their disease, but this subgroup (< 60 years, RA or RARS) was shown by IPSS analysis to have a median survival of more than 11 years without treatment. IPSS low and intermediate 1 risk categories thus hardly form an indication for early transplant, unless perhaps complex unfavourable cytogenetics or a life threatening single cytopenia is present.

Unrelated donor transplants are, at present, not indicated in this category. In the Seattle series on unrelated donor transplants the actuarial non-relapse mortality at 2 years for RA patients (n=20) was 46%. In Leuven also reported 50%. According to IPSS, these patients, if left untreated, can be predicted to have a 50% chance of survival beyond 11 years.

Moreover, if the total Seattle data on 241 transplanted patients were subjected to IPSS score evaluation, slightly more than half of their patients (n=145) belonged to intermediate-2 or high-risk categories before transplant and had a DFS of only 32 and 24%, respectively. This included sibling transplants.

As stated above, long-term DFS with chemotherapy alone in this category amounts to about 15%, with 16% death in aplasia.

Therefore definite recommendations regarding the early use of allogeneic transplants in MDS, outside well-con-

trolled and randomized studies, cannot be made.

Attempts at reducing the risk of TRM are urgently needed. Substitution of "supralethal" conditioning regimens by less toxic, tolerance-inducing chemotherapy supplemented with delayed lymphocyte infusions ("mini-transplants") may improve outcome considerably. The availability of large numbers of allogeneic peripheral blood stem cells—partially or totally T-cell depleted, with or without add-backs—offers new opportunities for improved transplant technology.

Autologous stem cell transplantation

The often unacceptably high toxicity of allogeneic transplantation, has prompted many investigators—encouraged by data obtained in AML—to explore the feasibility of autologous bone marrow or stem cell transplantation in both intermediate and high risk MDS patients.

The Chronic Leukemia Registry of the EBMT contains data on almost 200 patients autografted for MDS or secondary leukemia. Data on 79 of those transplanted in first complete remission were recently published. The 2-year overall survival, DFS and relapse rates were 39%, 34%, and 64%, respectively. Patients younger than 40 years had a significantly better DFS (39%) than patients older than 40 (25%). The large majority of these patients were transplanted for a secondary leukemia or therapy-related MDS, only 19 underwent auto BMT for a primary RAEB or RAEB-T. The survival of only the latter was slightly better (46%) than the whole group. The transplant related mortality was lower than 10%.

These data have to be interpreted with caution. Only patients in CR were included in this retrospective analysis, excluding those not recuperating from or resistant to induction chemotherapy. Moreover, no data are available on the number of patients with MDS in whom no adequate marrow harvest could be performed (persistent hypoplasia, fibrosis, poor performance, etc.).

Preliminary results on the influence of cytogenetic data on the outcome of autotransplant confirm previous data on intensive chemotherapy, i.e. actuarial 2-year survival of 52% in patients with good or intermediate risk, versus 28% in the poor risk group.

Encouraged by data obtained in AML and intrigued by the (sometimes very) delayed repopulation characteristics after bone marrow transplant, the feasibility of peripheral blood progenitor cell harvest and transplantation was also explored.

Even in high risk MDS, sufficient PBPC (i.e. > 10⁶ CD34/kg or > 10⁵ CFU-GM/kg) can be collected in first CR after priming with chemotherapy and G-CSF.

Reinfusion of these stem cells after myeloablative chemotherapy results in much faster and more complete recovery of granulocyte and platelet counts.

Consistent with this rapid recovery, days of fever, need for parenteral antibiotics, empiric antifungal therapy, transfusions of red cells and platelets, and total duration of hospitalisation are significantly decreased when compared

with a historical matched auto-BMT group.

Early relapse rates are not different from auto-BMT, while direct transplant-related mortality is less prominent. A major concern remains the possible contamination of the peripheral blood progenitor cells with clonal malignant cells. In our patients with chromosomal abnormalities at diagnosis, a normal karyotype and clinical and morphological CR state were required at the time of harvest. In addition we performed in depth clonality studies on the cells of female patients by the HUMARA assay, based on X-chromosome inactivation patterns.

Highly purified hematopoietic progenitor cell populations (CD34+CD38^{low}, CD34+CD38^{high}, CD34+CD33^{low}, CD34+CD33^{high}) were obtained and enriched from bone marrow and peripheral blood at diagnosis and post-remission induction and from the apheresis products.

An unequivocal polyclonal pattern could be shown to be reinstated by chemotherapy. PBPC harvests also could be demonstrated to contain polyclonal hematopoiesis both at the level of immature and committed precursors.

These data show that it is feasible to collect non-clonal, putative benign, CD34+ progenitors even from high risk MDS patients. Preliminary results seem to indicate that also in early stage MDS (RA or RARS) polyclonal hematopoiesis remains present and that polyclonal progenitors can be harvested with growth factors in steady state for future use. The early results of PBPC transplantation indicate that survival (not DFS) figures may approach those of allogeneic transplants and even surpass those of unrelated transplants, because of low TRM.

Relapse rates remain a major concern however. Whether PBPC transplants will improve survival rates over conventional high dose consolidation is at present under study.

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